UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MISSOURI
EASTERN DIVISION

IN RE CELEXA AND LEXAPRO	)	MDL DOCKET NO. 1736
PRODUCTS LIABILITY LITIGATION	)	ALL CASES

MEMORANDUM AND ORDER

The plaintiffs in this products liability Multi-District Litigation (MDL) allege that the antidepressants Celexa and Lexapro cause people to commit suicide. Defendant Forest makes, markets and sells these drugs. Out of the twelve cases remaining in this MDL, all but one involve adult decedents.[1] This matter is before me on Forest's motion to exclude plaintiffs' warnings expert, Michael Hamrell, Ph.D., from testifying when these remaining cases are returned to their transferor courts for trial [#626].[2] Forest asks me to find that this expert is not qualified to testify regarding the adequacy of Forest's warnings for Celexa and Lexapro and that his opinions are inadmissible because they are not based on any methodology. Forest's motion will be denied for the reasons that follow.

Discussion

Federal Rule of Evidence 702 and Daubert v. Merrell Dow Pharms., Inc.,

[1]The rest of the cases were settled.

[2]None of these cases were filed in this Court so I will not be trying any of them.

509 U.S. 579 (1993), govern the admissibility of expert testimony. The Daubert standard applies to all expert testimony, whether based on scientific competence or other specialized or technical expertise. See Polski v. Quigley Corp., 538 F.3d 836, 838 (8th Cir. 2008). Rule 702 provides:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Fed. R. Evid. 702. "[I]t is the responsibility of the trial judge to determine whether a particular expert has sufficient specialized knowledge to assist jurors in deciding the specific issues in the case." Wheeling Pittsburgh Steel Corp. v. Beelman River Terminals, Inc., 254 F.3d 706, 715 (8th Cir. 2001). "Once initial expert qualifications and usefulness to the jury are established, however, a district court must continue to perform its gatekeeping role by ensuring that the actual testimony does not exceed the scope of the expert's expertise, which if not done can render expert testimony unreliable . . . ." Id.

The expert's scientific, technical, or specialized knowledge must also "assist the trier of fact to understand the evidence or determine a fact in issue." Fed. R.

Evid. 702. I must ensure that "any and all scientific testimony or evidence admitted is not only relevant, but reliable." Daubert, 509 U.S. at 589. The function also serves "to make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." Kumho Tire Co., Ltd. v. Carmichael, 526 U.S. 137, 152(1999).

"[T]he requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." Daubert, 509 U.S. at 590. The Supreme Court explained that evidentiary reliability means trustworthiness. Id. at 591 n. 9. "Proposed testimony must be supported by appropriate validation— i.e., 'good grounds,' based on what is known." Id. at 590. "The standard for judging the evidentiary reliability of expert evidence is lower than the merits standard of correctness." Kuhn v. Wyeth, Inc., 686 F.3d 618, 624-625 (8th Cir. 2012) (internal quotation marks and citation omitted). "Proponents of expert testimony need not demonstrate that the assessments of their experts are correct, and trial courts are not empowered to determine which of several competing scientific theories has the best provenance." Id. at 625 (internal quotation marks and citations omitted). "Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof

are the traditional and appropriate means of attacking shaky but admissible evidence." Daubert, 509 U.S. at 596. "Rule 702 reflects an attempt to liberalize the rules governing the admission of expert testimony. The rule clearly is one of admissibility rather than exclusion." Lauzon v. Senco Prods., Inc., 270 F.3d 681, 686 (8th Cir. 2001) (internal quotation marks and citations omitted). "The exclusion of an expert's opinion is proper only if it is so fundamentally unsupported that it can offer no assistance to the jury." Wood v. Minn. Mining & Mfg. Co., 112 F.3d 306, 309 (8th Cir. 1997) (internal quotation marks and citation omitted).

The Supreme Court identified in Daubert a number of factors that might assist the district court in determining the admissibility of expert evidence: (1) whether the theory or technique applied can be tested, (2) whether the theory or technique has been subject to peer review or publication, (3) the known or potential rate of error, and (4) whether it is accepted in the relevant discipline. Id. at 593–94. It instructed me to focus on "principles and methodology, not on the conclusions that they generate." Id. at 595. The Court later recognized that "conclusions and methodology are not entirely distinct from one another." General Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997). Expert evidence may be excluded if the court determines "that there is simply too great an analytical gap

between the data and the opinion proffered." Joiner, 522 U.S. at 146.

Plaintiffs hired Dr. Hamrell to offer expert testimony about the adequacy of Celexa and Lexpro's labeling, as well as Forest's regulatory compliance in the pharmaceutical industry and pharmacovigilance activities related to post-marketing adverse event reporting. Forest argues that Dr. Hamrell is not qualified to testify as an expert in this case because he lacks the necessary experience or training. Dr. Hamrell earned a Bachelor of Science degree in biochemistry from the University of California, Los Angeles in 1973 and Ph.D. in pharmacology from the University of Southern California in 1977. Although not a medical doctor, he is by education and training a pharmacologist and a toxicologist. He was also awarded a Regulatory Affairs Certification from the Regulatory Affairs Professional Society (RAPS) in 1996 and was elected a RAPS fellow in 2009.[3]

Dr. Hamrell has more than 25 years experience in drug, biologic, and medical device regulatory affairs and has been involved with virtually "all aspects of product development in the pharmaceutical, biotech, and medical device industry." (Doc. # 634-1 at 2). Dr. Hamrell started his career as an Assistant Professor at McGill University in Montreal, Canada, then moved into the

[3]"RAPS is the largest global organization of and for those involved with the regulation of healthcare and related products, including medical devices, pharmaceuticals, biologics and nutritional products." See http://www.raps.org/.

pharmaceutical industry as a Drug Registration Manager in 1982 with Anaquest/BOC Group. While at Anaquest, Dr. Hamrell was responsible for regulatory affairs, including the preparation and submission of all regulatory applications, drug registration activities and regulatory guidance for the international market.

In 1985, Dr. Hamrell went to work at the FDA as a pharmacologist reviewer in the Division of Bioequivalence and the Division of Antiviral Drug Products. During his five years there, Dr. Hamrell was the primary reviewer for more than 50 Investigational New Drug Applications and New Drug Applications.[4] Dr. Hamrell also reviewed more than 200 bioequivalence studies for major drug products, which "provided [him] with a broad knowledge of the FDA regulatory requirements for manufacturing and clinical pharmacology and development of many classes of drugs." (Doc. # 6314-1 at 3). Dr. Hamrell also drafted FDA documents and position papers on the issues of bioequivalence and generic drugs, including a major policy paper on the FDA's position on bioequivalence that was published in a peer reviewed journal. While at the FDA, Dr. Hamrell's responsibilities included review of all safety data associated with any IND or NDA

[4]The IND is generally the first step toward seeking FDA approval for marketing a new drug to the public, whereas the NDA application is the vehicle through which drug companies formally propose that the FDA approval a new drug for sale and marketing in the United States.

application. He specifically reviewed the data submitted by pharmaceutical companies for safety information as part of his primary pharmacology/toxicology role at the FDA. Dr. Hamrell was also responsible for reviewing safety data such as adverse event reports submitted by pharmaceutical companies after drug approval. He also participated in safety reviews based on "signal" detection.[5]

Dr. Hamrell left the FDA in 1990 and joined the National Institutes of Health as the Chief of the Regulatory Affairs Section for the Division of AIDS/NIAID. As the senior regulatory affairs person for his division, Dr. Hamrell was responsible for all regulatory and compliance activities for a network of multi-center groups conducting clinical trials for AIDS treatment. He managed a staff in the submission of more than 50 INDs each year as well as coordinated all regulatory aspects for four multi-center trials including drugs and biologics being carried out at approximately 200 different worldwide clinical sites.

From 1992-1993, Dr. Hamrell was the Director of Worldwide Regulatory Affairs for a biotech company named Vestar. In addition to pharmacological and toxicological responsibilities, he was also responsible for all worldwide regulatory activities including all regulatory submissions for the company. He provided

[5]This refers to looking at reported adverse reactions to determine if they signal a potential problem with a drug.

guidance to the company about regulatory requirements for product registration, marketing, safety and adverse event reporting.

In 1994, Dr. Hamrell started his own consulting company, Moriah Consultants. This firm provides comprehensive regulatory affairs consulting and training for the pharmaceutical, biotechnical, and medical device industries. Dr. Hamrell is typically retained by pharmaceutical companies for negotiating and dealing with the FDA on regulatory strategies for submissions, clinical studies, and post-approval issues. In conjunction with his consulting work, Dr. Hamrell analyzes and uses the FDA's adverse event reporting system database to advise his clients about safety related issues.

Dr. Hamrell has extensively published on regulatory issues. In addition to the papers published while at the FDA, Dr. Hamrell also published peer-reviewed literature regarding prescription drug labeling. In 2000, Dr. Hamrell published an article entitled "Current Regulations and Practices for Adverse Event Reporting: Implications for Labeling" in Drug Information Journal, a peer-reviewed publication. This article discussed federal drug regulations, requirements for prescription drug warnings, drug labeling in compliance with federal regulations, and safety issues. A review of Dr. Hamrell's expert report also reveals numerous other publications about drug regulatory issues. (Doc. # 634-1 at 31-35). Dr.

Hamrell has also served as adjunct professor, instructor, and lecturer on regulatory affairs at several universities across the country, and he currently teaches pharmacology, drug development, regulatory affairs, clinical research and regulatory compliance at five universities. (Doc. # 634-1 at 30). He has also made numerous presentations on regulatory matters (Doc. # 634-1 at 37-46), is a member of several professional societies (Doc. # 634-1 at 30), and has served as past editor-in-chief and current editorial board member of multiple professional regulatory publications (Doc. # 634-1 at 30).

Despite Dr. Hamrell's impressive credentials, Forest argues that he is not qualified to render expert opinion in this case because his job at the FDA did not include drafting warning labels or statistics, and he has no specific experience with antidepressants or suicidality. These arguments are meritless and do not preclude Dr. Hamrell from being qualified to testify as a warnings expert in this case. First, as shown above Dr. Hamrell's experience is not limited solely to his time at the FDA, and the combination of his qualifications and his extensive experience and training in both the public and private sectors regarding regulatory compliance and safety issues provide him with specialized knowledge that will assist a jury at trial. Moreover, Dr. Hamrell did participate in the review of warnings labels, as well as post-marketing drug safety data, while at the FDA as

part of the safety team. That he was not directly responsible for drafting a label does not mean that he should not be permitted to testify regarding the adequacy of warnings labels, particularly where Dr. Hamrell's focus at the FDA was on the very safety issues that necessitate the need for warnings labels (or changes). Forest also makes much out of the fact that Dr. Hamrell does not have any prior experience with antidepressants and suicidality specifically, but that does not render him unqualified to testify as an expert here. Dr. Hamrell relied upon Dr. Healy's expert report for background information regarding this issue, which is both a common and an appropriate practice for an expert.[6] Dr. Hamrell is familiar with the FDA regulations regarding safety issues, including updating safety information prior to drug approval and post-marketing pharmacovigilance expectations and regulations generally, and his testimony regarding these issues will be helpful to a jury deciding whether Forest should have suggested warnings label changes based on data suggesting a link between antidepressants and suicide.

Nor is Dr. Hamrell unqualified merely because, as Forest suggests, he does not know specifically what Forest or the FDA knew about the link between antidepressants and suicide during the relevant time period. As plaintiffs point

[6]Since I am also denying Forest's motion to exclude Dr. David Healy, I find no error in Dr. Hamrell's reliance on Dr. Healy's expert report here.

out, this argument does not render Dr. Hamrell unqualified to testify as an expert because his opinions focus on what Forest should have known or done based on the data available to them, not what the FDA or Forest actually did. Plaintiffs' theory of the case is that under FDA regulations, Forest was obligated to monitor this adverse event data and could have (and should have) proposed changes to its warnings labels on Celexa and Lexapro, irrespective of FDA action. Certainly Forest can cross-examine Dr. Hamrell about what actions the FDA took (or did not take) during the relevant time period, but the mere fact that Dr. Hamrell did not consider this information does not render him unqualified to testify at trial.

Dr. Hamrell is qualified to testify as an expert in this case based upon his education, training, and experience, and Forest's motion to exclude on this basis will be denied.

Next, Forest argues that Dr. Hamrell should be excluded as an expert because his opinions are not based upon any methodology. Dr. Hamrell offered the following expert opinions:

> 1. It is appropriate to review SSRI data collectively when evaluating safety issues.
>
> 2. Post Marketing adverse event data shows strong signals of a relationship between Celexa/Lexapro and suicidal behavior.
>
> 3. The Lexapro and Celexa labels were inadequate at all times prior to

> 2005 and by June 30, 2001, Forest should have enhanced the warnings for suicidality.
>
> 4. The FDA review does not establish that Celexa and Lexapro do not increase the risk of suicidality in adults.

(Doc. # 634-1at 5). Dr. Hamrell opined that, given the information available to Forest in June 2001, the following boxed label for Celexa and Lexapro would have been appropriate:

> Lexapro may increase the risk compared to placebo of suicidal thinking and behavior (suicidality). Anyone considering the use of Lexapro must balance this risk with the clinical need. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on Lexapro therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use)

(Doc. # 634-1 at 18). Dr. Hamrell based his opinions "in part upon my education, personal experience, and review of documents disclosed during the pendency of litigation, includ[ing] but not limited to sources containing adverse events associated with Selective Serotonin Reuptake Inhibitors, the defendant's internal research and reports, Spontaneous Reporting System (SRS), Adverse Event Reporting System (AERS), FDA records, international regulatory efforts, the

expert reports for Plaintiff's other expert (Dr. David Healy), medical literature, deposition transcripts and exhibits." (Doc. # 634-1 at 2). Contrary to Forest's suggestion, Dr. Hamrell did not base his opinions "exclusively upon a simple rough count of adverse events plaintiffs' counsel provided him," so Forest's motion to exclude on this basis will be denied.

Forest complains that Dr. Hamrell did not use a "methodology," but the advisory notes to Rule 702 make clear that "some types of expert testimony will not rely on anything like a scientific method, and so will have to be evaluated by reference to other standard principles attendant to the particular field of expertise. [In those cases I] must find that it is properly grounded, well-reasoned, and not speculative before it can be admitted." Fed. R. Civ. P. 702 Advisory Committee Note. Moreover, the Eighth Circuit Court of Appeals has held that "[t]here is no single requirement for admissibility [of expert testimony] as long as the proffer indicates that the expert evidence is reliable and relevant." In re Prempro Prods. Liab. Litig., 586 F.3d 547, 565 (8th Cir. 2009).

Here, Dr. Hamrell reviewed all the materials summarized above (including but not limited to adverse event reports) and, applying his education, training and experience, concluded that, as of June 2001, Forest should have seen a causal relationship between Celexa/Lexapro and acted on its own initiative to strengthen

the warning labels. Dr. Hamrell testified that drug manufacturers had the obligation to monitor postmarketing safety data and the ability to enhance warning labels without prior FDA approval, and that the regulations do not require proof of a causal relationship between a serious hazard and a drug before a warning label revision is required. In reaching this conclusion, Dr. Hamrell used the same type of methodology or analysis that he used while at the FDA and in the private sector. He reviewed the SSRI data collectively,[7] the pharmacovigilance evidence that was available to Forest, including post-marketing safety data, regulatory requirements and expectations, and the testimony of Forest's pharmacovigilance witness. Dr. Hamrell identified three distinct time periods and explained how the data from the FDA AERS data was culled, which types of reports were included, why those types of reports were included, and the basis for segmenting them in the manner that he did. He then provided the resultant data tables that were produced and applied his education, experience and training to conclude that, in his opinion, the adverse event reports were sufficient evidence to constitute a safety signal and trigger a warning label change from Forest.[8] In Dr. Hamrell's experience, the

[7]In denying the motion to exclude Dr. Healy, I explained that this approach was permissible. Plaintiffs also point out that Forest's head of pharmacovigilance also agreed that this approach was appropriate.

[8]I reject Forest's suggestion that Dr. Hamrell's opinion should be excluded simply because someone else actually ran the computer program that provided the data. Dr. Hamrell

FDA would have allowed the change because it relies upon pharmaceutical companies to analyze safety data. Dr. Hamrell's testimony is properly grounded and well-reasoned, and he reached his conclusions looking at the same type of data and using the same methods he used while at the FDA and that he continues to regularly employ in the private sector. Forest's challenges to Dr. Hamrell's methodology are really just disagreements with his conclusions about the significance of the safety data and are fodder for cross-examination. Dr. Hamrell's methodology is sufficiently reliable to pass the threshold test of admissibility. As such, Forest's motion to exclude will be denied.

As for Forest's argument that some of the plaintiffs' claims should be dismissed for failure to have a warnings expert, these issues are not common to all cases and are therefore not properly before me. Instead they should be raised before the appropriate trial courts when these cases are returned for trial. The same is true with respect to plaintiff Tammy Muzichuck's motion for judgment on the pleadings. As this motion relies on West Virginia law, it is not appropriate for consideration by me and instead should be raised before the trial judge when these cases are returned for trial.

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personally performed quality control on the data that was provided. Forest may challenge the adequacy of his quality control on cross-examination, but the mere fact that he did not personally cull the data does not mean that his expert testimony should be excluded.

Finally, it appears that all common issues have been resolved, and that these cases may be ready to be returned to their transferor courts for any remaining case specific discovery, motion practice, and trial. I would like the parties to file a joint memorandum by March 15, 2013, advising the Court whether any issues appropriate for resolution by this MDL court remain and, if so, an explanation of what those issues are and a proposed schedule for completion of these issues. If the parties agree that the cases are ready to be returned for trial, then I would like them to prepare a joint proposed Order of Remand for the Court's consideration and to propose a date by which the proposed Order will be filed. Once I receive the joint memorandum, I will set a status conference to address these, and any remaining, issues.

Accordingly,

IT IS HEREBY ORDERED that defendant's motion to exclude the testimony of Michael Hamrell, Ph.D. [#626] is denied.

IT IS FURTHER ORDERED that plaintiff's motion for judgment on the pleadings [#622] is denied without prejudice.

IT IS FURTHER ORDERED that the parties shall file a joint memorandum as set out above by **March 15, 2013.**

RODNEY W. SIPPEL
UNITED STATES DISTRICT JUDGE

Dated this 4th day of March, 2013.